REMARKS

Claims 66 to 69, 72 to 74, 82, 115 to 119, 121, 123 to 128, 130, 131, 134 to 143, 145, 147 to 152, 154, 155 and 158 to 165 are pending in the subject application and claims 120, 122, 144, 146 and 166 to 171 have been withdrawn. Applicants have herein canceled claims 66 to 69, 72 to 74, 82, 115 to 128, 130, 131, 134 to 152, 154, 155 and 158 to 171 and have added claims 172 to 211.

The subject application is a continuation of U.S. Serial No. 10/346,853, filed January 17, 2003, which is a continuation of U.S. Serial No. 09/100,812, filed June 19, 1998, now U.S. Patent No. 6,573,099 B2, issued June 3, 2003, which claims priority of Australian Provisional Patent Application No. PP2492, filed March 20, 1998 (the "Priority Application"). A certified copy of the Priority Application was filed on September 22, 1998 in U.S. Serial No. 09/100,812. Applicants attach hereto as **Exhibit A** a copy of the Priority Application for the Examiner's convenience.

Support for new claims 172, 188 and 200 can be found, *inter alia*, at page 3, line 24, to page 4, line 1; page 6, lines 17 to 25; page 7, lines 17 to 20; page 8, line 21; page 10, lines 10 and 17; page 11, line 28, to page 12, line 1; page 12, lines 18 to 20; page 13, lines 11 to 13; page 14, lines 6 to 9; page 16, lines 17 and 18; page 19, lines 14 and 15, and lines 21 and 22; page 22, lines 12 to 14; page 23, lines 9 and 10; and page 23, lines 17 to 19, of the subject application, and on the same pages and lines of the Priority Application.

Support for new claims 173 and 174 can be found, *inter alia*, at page 16, lines 20 to 26; and page 17, lines 4 and 5, of the subject application, and on the same pages and lines of the

Priority Application.

Support for new claims 175, 189 and 201 can be found, *inter alia*, at page 8, lines 21 and 22, of the subject application, and on the same pages and lines of the Priority Application.

Support for new claims 176, 190 and 202 can be found, *inter alia*, at page 16, line 26, to page 17, line 2, of the subject application, and on the same pages and lines of the Priority Application.

Support for new claims 177, 191 and 203 can be found, *inter alia*, at page 7, lines 25 to 27, of the subject application, and on the same pages and lines of the Priority Application.

Support for new claims 178, 192 and 204 can be found, *inter alia*, at page 7, lines 25 to 28, of the subject application, and on the same pages and lines of the Priority Application.

Support for new claims 179, 193 and 205 can be found, *inter alia*, at page 7, lines 25 and 26, of the subject application, and on the same pages and lines of the Priority Application.

Support for new claims 180, 194 and 206 can be found, *inter alia*, at page 8, lines 6 to 7, of the subject application, and on the same pages and lines of the Priority Application.

Support for new claims 181, 182, 195, 196, 207 and 208 can be found, *inter alia*, at page 19, lines 24 and 25, of the subject application, and on the same pages and lines of the Priority Application.

Support for new claims 183, 197 and 209 can be found, *inter alia*, at page 19, lines 24 to 26, of the subject application, and on the same pages and lines of the Priority Application.

Support for new claims 184, 198 and 210 can be found, *inter alia*, at page 17, lines 20 to 22, of the subject application, and on the same pages and lines of the Priority Application.

Support for new claims 185 and 186 can be found, *inter alia*, at page 23, lines 9 to 11, of the subject application, and on the same pages and lines of the Priority Application.

Support for new claims 187, 199 and 211 can be found, *inter alia*, at page 23, lines 21 to 24, of the subject application, and on the same pages and lines of the Priority Application.

Applicants have canceled claims 66 to 69, 72 to 74, 82, 115 to 128, 130, 131, 134 to 152, 154, 155 and 158 to 171 without prejudice to applicants' right to prosecute these claims in this or related application. After entry of this Amendment, claims 172 to 214 will be pending and under examination.

Election/Restrictions

The January 8, 2008 Final Office Action alleged that this application contains new claims 166-171 drawn to an invention nonelected with traverse in the reply filed on 10/31/06, and indicated that a complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 C.F.R. § 1.144), referencing M.P.E.P. § 821.01.

The January 8, 2008 Final Office Action indicated that claims

120, 122, 144, and 146 allegedly reciting a target gene encoding a viral DNA polymerase, viral coat, or a visually-detectable gene in claims 163-165 remain withdrawn from further consideration pursuant to 37 C.F.R. § 1.142(b) as being drawn to an alleged nonelected species, there being no allowable generic or linking claim, and alleged that election was made without traverse in the reply filed on 12/29/06.

Applicants' Response

In response to the allegations regarding claims 166 to 171, without conceding the accuracy of the Examiner's position and without prejudice to applicants' right to pursue these claims in this or a related application, applicants have canceled claims 166 to 171.

In response to the allegation that applicants elected a species *without traverse* in the December 29, 2006 Amendment, applicants point out that the election in the December 29, 2006 Amendment was made without prejudice (page 13, first paragraph, of the December 29, 2006 Amendment) but *with* traverse (page 12, third paragraph, of the December 29, 2006 Amendment).

To advance prosecution, however, and without conceding the accuracy of the allegations in the January 8, 2008 Final Office Action, applicants have canceled claims 120, 122, 144, 146 and 163 to 165.

By this Amendment, applicants are presenting a rewritten version of the examined claims. Specifically, the claims presented herein recite "viral RNA polymerase," as well as non-elected species. Pursuant to M.P.E.P. § 809, *et seq.*, applicants

understand that the elected species of "viral RNA polymerase" is being examined and look forward to the examination of the other species upon allowability of the elected species.

Information Disclosure Statement

The Examiner indicated that the information disclosure statement (IDS) submitted on 10/25/07 was filed after the mailing date of the non-final rejection on 4/25/07. The Examiner indicated that the submission is in compliance with the provisions of 37 C.F.R. § 1.97, and was considered.

However, the Examiner alleged that the information disclosure statement filed 10/25/07 failed to comply with the provisions of 37 C.F.R. §§ 1.97, 1.98 and M.P.E.P. § 609 because several of the articles are missing the title and/or date. The Examiner indicated that such items had been placed in the application file, but the information referred to therein has not been considered as to the merits. The Examiner advised applicants that the date of any re-submission of items or missing information will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 C.F.R. § 1.97(e), referencing M.P.E.P. § 609.05(a).

Applicants' Response

In response, applicants refer the Examiner to the Supplemental Information Disclosure Statement below, and respectfully request consideration of all items disclosed.

Priority

The Examiner objected to the oath submitted January 15, 2004 in connection with the subject application. The Examiner alleged that it is not apparent if the oath incorrectly lists the foreign document as PP 2292. The Examiner alleged that the number of the foreign document appears to be PP 2492, referencing document in parent application (09/100,812 and 10/346,853).

The Examiner alleged that the foreign application PP2492 cited in the cross reference on page 1 of the specification is disclosed in an application data sheet, but is not disclosed in the oath. The Examiner noted that a petition for unintentionally delayed claim for priority under 37 C.F.R. § 1.78(a)(3) filed on 12/28/06 in the parent application (10/346,853) is pending. The Examiner alleged that Exhibit A disclosing the oath for application 09/646,807 is moot since this application is not related to that application.

Applicants' Response

In response, applicants initially thank the Examiner for the careful review. The priority paragraph of the subject application correctly recites "Australian Provisional Patent Application No. PP2492" (emphasis added). Applicants have attached a copy of the priority paragraph of the subject application hereto as **Exhibit B** for the Examiner's reference.

The error in the Declaration submitted January 15, 2004 was a typographical error. Pursuant to 37 C.F.R. § 1.76(d)(1), applicants attach hereto as **Exhibit C** an Application Data Sheet

identifying the correct priority information. According to 37 C.F.R. § 1.76(d)(1) the attached Application Data Sheet governs notwithstanding the priority information in the earlier filed Declaration, thereby addressing the Examiner's objection.

Claim Rejections Under 35 U.S.C. § 112 - Written Description Requirement

The January 8, 2008 Final Office Action on pages 3 to 7 rejected claims 66-69, 72, 82, 115-119, 121, 123-128, 130, 131, 134-143, 145, 147-152, 154, 155, and 158-165 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner alleged that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants' Response

In response, without conceding the accuracy of the Examiner's position and without prejudice to applicants' right to pursue the subject matter of the claims in this or a related application, applicants have canceled claims 66 to 69, 72, 82, 115 to 119, 121, 123 to 128, 130, 131, 134 to 143, 145, 147 to 152, 154, 155 and 158 to 165, thereby making the rejection moot.

Applicants note that claims 66 to 69, 72, 82, 115 to 119, 121, 123 to 128, 130, 131, 134 to 143, 145, 147 to 152, 154, 155 and 158 to 165 were rejected, at least in part, based on the use of the term "substantially identical." Applicants' rewritten claims herein do not recite the term "substantially identical".

Claim Rejections Under 35 U.S.C. § 102 (e) - Fire et al.

The Examiner rejected claims 66, 67, 68, 69, 72, 73, 74, 82, 115, 117-119, 121, 123-125, 128, 130-131, 134-139, 141-143, 145, 147, 148, 149, 152, 154-155 and 158-165 under 35 U.S.C. § 102(e) as allegedly anticipated by Fire et al. (U.S. 6,506,559, cited on a PTO-1449).

Applicants' Response

In response, without conceding the accuracy of the Examiner's position and without prejudice to applicants' right to pursue the subject matter of the claims in this or a related application, applicants have canceled claims 66 to 69, 72 to 74, 82, 115, 117 to 119, 121, 123 to 125, 128, 130, 131, 134, 139, 141 to 143, 145, 147 to 149, 152, 154, 155 and 158 to 165 herein. Therefore, the rejection under 35 U.S.C. § 102 is moot. Furthermore, the rejection cannot apply to the rewritten claims presented herein for the following reasons.

Initially, applicants respectfully point out that U.S. Patent No. 6,506,559 to Fire et al. ("the '559 Patent") is not prior art to the subject application. Applicants note that the first effective filing date of the rewritten claims herein is March 20, 1998. The '559 Patent issued from an application filed December 18, 1998, i.e. *after* the first effective filing date of the subject application.

The '559 Patent does claim the benefit of U.S. Provisional Application No. 60/068,562, filed December 23, 1997 (the "Fire et al. Provisional"). The Fire et al. Provisional, however,

discloses less than the '559 Patent. Accordingly, any rejection under 35 U.S.C. §§ 102 and 103 can at most be based on the disclosure of the Fire et al. Provisional, not on the disclosure of the '559 Patent. As explained below, the Fire et al. Provisional does not disclose at least each of the following elements of applicants' claims: 1) targeting a "viral RNA polymerase"; 2) "20-30 consecutive nucleotides" identical to a region of the target gene; and 3) a "stuffer fragment".

It is clear on the present record that the Fire et al. Provisional does not disclose a construct having a nucleotide sequence identical to a target gene encoding a "viral RNA polymerase". In fact, the '559 Patent also does not disclose such a construct. For this reason alone the pending claims are novel over the Fire et al. Provisional.

Additionally, the Fire et al. Provisional does not disclose a "stuffer fragment". In the January 8, 2008 Final Office Action at page 8, lines 21 to 23, the Examiner alleged that "[a] single self-complementary strand would indicate that the two nucleotides are sequences which would read on a stuffer between the two sequences." As discussed above, the '559 Patent is not prior art to the subject application. Applicants note that page 6, lines 18 to 20, of the Fire et al. Provisional contains the disclosure: "[t]he double-stranded structure may be formed by a single self-complementary RNA strand or multiple complementary RNA strands." Applicants respectfully submit that this portion of the Fire et al. Provisional is a *disclosure*; this disclosure does not and cannot "read on" a stuffer fragment. This disclosure also does not teach a stuffer fragment.

Applicants note that in the January 8, 2008 Final Office Action

at page 11, line 17, the Examiner acknowledged that the '559 Patent does not disclose a "stuffer sequence of nucleotides 10-50 nucleotides in length." Applicants respectfully submit that the Fire et al. Priority document does not disclose the stuffer fragment recited in any one of claims 181-183, 198-200, or 213-215.

Applicants therefore maintain that the claims presented herein are clearly novel over the Fire et al. Provisional.

In the interest of compact prosecution, applicants also point out that the claimed construct cannot be obvious over the Fire et al. Provisional because the claimed construct must have a "first nucleotide sequence of 20-30 consecutive nucleotides identical" to a region of the target gene in a mammalian cell.

Applicants are aware that on page 7, lines 7 to 9, the Fire et al. Provisional states that "[t]he length of the identical nucleotide sequences may be at least 25, 50, 100, 200 or 400 nucleotides." Regardless of the proper complete meaning of this sentence in the Fire et al. Provisional, the sentence clearly does not differentiate between lengths. That is, based on this sentence, one of skill in the art would understand a length of the identical nucleotide sequences of 25 nucleotides to be no different than a length of 400 nucleotides.

Furthermore, the examples of the Fire et al. Provisional teach using identical nucleotide sequences that are much longer than what applicants claim in this application. Upon studying the examples in the Fire et al. Provisional, which are in *C.*

elegans[1], one of skill in the art would find that Table 1 on pages 22 and 23 teaches the use of identical nucleotide sequences of *at least* 299 nucleotides[2] to as high as 1033 nucleotides in animals. Based on the examples of the Fire et al. Provisional, one of skill in the art would conclude that the Fire et al. Provisional preferred at least 299 nucleotide long identical nucleotide sequences over shorter identical nucleotide sequences in animals.

Applicants' claims presented herein recite the range of 20-30 consecutive nucleotides identical to a region of a target gene in a mammalian cell. This is an optimal range *in mammalian cells*. Applicants attach hereto a copy of Paul, C.P., et al., (2002) "Effective expression of small interfering RNA in human cells," Nat. Biotechol. 20(5):505-508 as **Exhibit D**, which was published after the priority date of the subject application. Paul et al. on page 505 in the Abstract at lines 6 to 8 state that "uninterrupted RNA duplexes *longer than 30 base pairs* trigger generalized cellular responses through activation of dsRNA-dependent protein kinases" (emphasis added; citation in original omitted). Applicants maintain that the optimal range in *mammalian* cells of 20-30 contiguous nucleotides as claimed herein could not have been predicted from the prior art. As the

[1] *C. elegans* are animals, but *C. elegans* are not mammals.

[2] Referring to Figure 1, the Fire et al. priority document states at page 8, lines 15 to 18:

> Each segment tested for RNAi is designated with the name of the gene followed by a single letter (e.g., *unc22C*). Segments derived from genomic DNA are shown above the gene, segments derived from cDNA are shown below the gene. The consequences of injecting double-stranded RNA segments for each of these genes is described in Table 1. (Emphasis added.)

Table 1 contains columns labeled "Gene and Segment" and "Size". Therefore, Table 1 identifies i) the segments used including source; and ii) the length of the particular segment.

Examiner is aware, M.P.E.P. § 2144.05(II)(A) generally provides that differences in a range of a variable will not support the patentability of subject matter unless there is evidence indicating that the range claimed is unpredictably optimal. Applicants were the first to disclose a "nucleotide sequence of 20-30 contiguous nucleotides identical" to a region of a target gene in mammalian cells. This range is unpredictably optimal. Accordingly, applicants' claimed invention reciting the optimal range of 20-30 contiguous nucleotides could not have been predicted from the prior art.

On this basis alone the claimed invention cannot be obvious over Fire et al.

Furthermore, the Fire et al. Provisional teaches away from the claimed invention. As the Examiner is aware, prior art must be considered in its entirely, including disclosure that teaches away from the claimed invention. *See, e.g.* M.P.E.P. § 2141.02. Regardless of the proper meaning of the sentence on page 7, lines 7-9, of the Fire et al. Provisional, the examples teach using nucleotide lengths of 299 nucleotides to 1033 nucleotides in animals, as explained hereinabove. By example, therefore, the Fire et al. Provisional discourages the use of sequences of identical nucleotides of only 20-30 nucleotides in animals. Accordingly, applicants maintain that Fire et al. teach away from the claimed invention.

Claim Rejections Under 35 U.S.C. § 103 - Fire et al. taken with Ladner et al.

The Examiner rejected claims 68, 126, 138, and 150 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Fire et al.

(U.S. 6,506,559, cited on a PTO-1449) taken with Ladner et al. (US 5,198,346).

Applicants' Response

In response, without conceding the accuracy of the Examiner's position and without prejudice to applicants' right to pursue the subject matter of the claims in this or a related application, applicants have canceled claims 68, 126, 138 and 150, thereby rendering the rejection moot.

Moreover, the combination of Fire et al. and Ladner et al. cannot render obvious the claims presented herein at least because the combination does not teach or suggest targeting "viral RNA polymerase," or using "20-30 contiguous nucleotides" in a "mammalian cell", as recited in the pending claims. Accordingly, applicants maintain that the rejection of the previously presented claims under 35 U.S.C. § 103 as allegedly obvious over Fire et al. and Ladner et al. cannot be applied to the claims presented herein.

Claim Rejections Under 35 U.S.C. § 103 - Fire et al. taken with German et al.

The Examiner rejected claims 68, 127, 138, and 151 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Fire et al. (U.S. 6,506,559, cited on a PTO-1449) taken with German et al. (U.S. 6,225,290).

Applicants' Response

In response, without conceding the accuracy of the Examiner's

position and without prejudice to applicants' right to pursue the subject matter of the claims in this or a related application, applicants have canceled claims 68, 127, 138 and 151, thereby rendering the rejection moot.

Moreover, the combination of Fire et al. and German et al. cannot render obvious the claims presented herein at least because the combination does not teach or suggest targeting "viral RNA polymerase," or using "20-30 contiguous nucleotides" in a "mammalian cell", as recited in the pending claims. Accordingly, applicants maintain that the rejection of the previously presented claims under 35 U.S.C. § 103 as allegedly obvious over Fire et al. and German et al. cannot be applied to the claims presented herein.

Claim Rejections Under 35 U.S.C. § 103 - Fire et al. taken with Cowsert et al.

The Examiner rejected claims 68, 116, 139, and 140 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Fire et al (U.S. 6,506,559, cited on a PTO-1449) taken with Cowsert et al. (U.S. 5,580,767).

Applicants' Response

In response, without conceding the accuracy of the Examiner's position and without prejudice to applicants' right to pursue the subject matter of the claims in this or a related application, applicants have canceled claims 68, 116, 139 and 140, thereby rendering the rejection moot.

Moreover, the combination of Fire et al. and Cowsert et al. cannot render obvious the claims presented herein at least because the combination does not teach or suggest targeting "viral RNA polymerase," or using "20-30 contiguous nucleotides" in a "mammalian cell", as recited in the pending claims. Accordingly, applicants maintain that the rejection of the previously presented claims under 35 U.S.C. § 103 as allegedly obvious over Fire et al. and Cowsert et al. cannot be applied to the claims presented herein.

Double Patenting

The Examiner rejected claims 66-69, 72-74, 82, 115-119, 121, 123-128, 130, 131, 134-143, 145, 147-152, 154, 155, and 158-165 on the alleged ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 11-15, and 19-21 of Patent No. 6,573,099. The Examiner alleged that although the conflicting claims are not identical, they are not patentably distinct from each other because both set of claims are directed to a construct capable of producing dsRNA.

The Examiner indicated that applicants' arguments filed 10/25/07 have been fully considered but they are allegedly not persuasive. The Examiner alleged that in response to applicants' argument that the amendment to the claims overcomes the rejection, the argument is not found persuasive because the claims either read on the instant claims or are an obvious variant of the claims from '099. The Examiner alleged that in addition, other than reciting the amendment to the claims, the applicant does not argue how the claims are not obvious of the claims from '099.

The Examiner alleged that it is noted that applicants request

that the rejection be held in abeyance pending indication of allowable subject matter in the instant application or the resolution of reexamination of the '099 patent.

The Examiner provisionally rejected claims 66-69, 72-74, 82, 123-128, 130-131, 134-138, 147-152, and 158-162 on the alleged ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 56, 59, 60, 62, 63, 65-67, 77-101, and 107 of copending Application No. 09/646,807. The Examiner alleged that although the conflicting claims are not identical, they are not patentably distinct from each other because both set of claims read on an animal cell comprising a construct comprising two identical sequences to a target gene in an animal.

The Examiner indicated that this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The Examiner indicated that Applicants' arguments filed 10/25/07 have been fully considered but they are allegedly not persuasive.

The Examiner alleged that it is noted that applicants request that the rejection be held in abeyance pending indication of allowable subject matter in the instant application or the resolution of reexamination of the '099 patent.

The Examiner provisionally rejected claims 66-69, 72-74, 82, 123-128, 130-131, 134-138, 147-152, and 158-162 on the alleged ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims from copending Application Nos. 10/346,853, 10/646,070, and 11/364,183. The Examiner alleged that although the conflicting claims are not identical,

they are not patentably distinct from each other because both sets of claims read on an animal cell comprising a construct comprising two identical sequences to a target gene in an animal.

The Examiner indicated that this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The Examiner indicated that applicants' arguments filed 10/25/07 have been fully considered but they are allegedly not persuasive.

Applicants' Response

Applicants thank the Examiner for his note of applicants' request that the rejections be held in abeyance pending indication of allowable subject matter in the instant application or the resolution of reexamination of the '099 patent. Applicants respectfully maintain this request.